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| 10/693,252 | 10/24/2003 | Thomas J. Meade | 068269-5010-US | 9088 |
| 67374 7590 07/03/2008 MORGAN, LEWIS & BOCKIUS, LLP ONE MARKET SPEAR STREET TOWER SAN FRANCISCO, CA 94105 | | | | |
| EXAMINER | | | | |
| SCHLIENTZ, LEAH H | | | | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/693,252

Applicant(s)

MEADE ET AL.

Examiner

Leah Schlientz

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 January 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 19-23 and 26-36 is/are pending in the application.
- 4a) Of the above claim(s) 23, 26-28 and 30-36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 19-22 and 29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 24 October 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 1/10/2008, in reply to the Office Action mailed 7/12/2007, is acknowledged and has been entered. Claims 19 and 20 have been amended. Claims 24 and 25 have been cancelled. Claims 19 – 23 and 26 – 36 are pending, of which claims 21, 22, 26 – 28 and 30 - 36 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 19 – 22 and 29 are readable upon the elected invention and are examined herein on the merits for patentability.

Response to Arguments

Applicant's arguments, see page 7 of the Response, with respect to the rejection of claims 19 and 21 under 35 U.S.C. 112, first paragraph, have been fully considered but they are not persuasive for reasons set forth hereinbelow.

Applicant's arguments, see page 8 of the Response, with respect to the rejection of claims 19 and 21 under 35 U.S.C. 112, second paragraph, have been fully considered. The rejection has been WITHDRAWN as being overcome by amendment.

Applicant's arguments, see page 8 of the Response, with respect to the rejection of claims 20, 22, 25 and 29 under 35 U.S.C. 112, second paragraph, have been fully considered. The rejection has been WITHDRAWN as being overcome by amendment.

Applicant's arguments, see pages 8 – 10 of the Response, with respect to the rejection of claims 20, 22, 25 and 29 under 35 U.S.C. 102(e) as being anticipated by Lauffer (US 6,709,646) have been fully considered, but they are not persuasive for reasons set forth hereinbelow.

Applicant's arguments, see pages 10 – 11 of the Response, with respect to the rejection of claims 19 – 22, 25 and 29 under 35 U.S.C. 103(a) as being unpatentable over Lauffer (US 6,709,646) in view of Netzel-Arnett *et al.* (*Biochem.*, 1993, 32, p. 6427-6432), have been fully considered but they are not persuasive for reasons set forth hereinbelow.

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 19 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reasons set forth in the Office Action mailed 7/12/2007.

Applicant argues on page 7 of the Response that the specification provides adequate written description support for practicing the claimed invention. Applicant contends that the specification provides multiple representative examples, including working examples of representative MRI compounds, such that one of ordinary skill would have no doubt that Applicants were in possession of the invention as claimed at the time the invention was filed.

This is found non-persuasive. Applicant's limited disclosure of such a small number of representative amino acid sequences does not provide support that applicant was in possession of a reasonable number of species of the claimed genus to substantiate claiming such a broad genus. For example, the instantly claimed genus may include millions and millions of potential peptide sequences. While it is clear that applicant envisaged a few representative MMP recognizable peptide sequences and their conjugation to a DOTA macrocycle, such a few representative examples does not provide support that applicant had support for the millions and millions of possible sequences which may or may not be expected to have MMP recognition activity due to the drastic variety of structure/functional activity possibilities represented by such a genus.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 20, 22 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Lauffer *et al.* (US 6,709,646) for reasons set forth in the Office Action mailed 7/12/2007.

Applicant argues on pages 8 – 10 of the Response that “there is no indication in Lauffer that cleavage of the MS would result in a subsequent decrease in the T₁ of the IEM,” and that “there is no further disclosure in Lauffer with respect to cleavage of the MS and the remaining composition following administration of the compound and any subsequent change in T₁ of the chelator.” Applicant submits that components of the claimed invention possess a unique functional characteristic that is not present in the prior art, i.e. a change in T₁ of the MRI agent following cleavage of the MMP active peptide.

This is found non-persuasive. It is the position of the examiner that the compounds disclosed by Lauffer inherently affect T₁ reduction upon activation by MMP enzyme. See examples IIIb – IV (column 36 – 38). Lauffer discloses a chelator conjugated to an alkaline phosphatase-activated MS (Prodrug 1), which is hydrolyzed at the MS upon activation by alkaline phosphatase to form activated contrast agent 8. Compound 8 “bound ... to HSA with a greater affinity than prodrug 1 and with a higher relaxivity. The higher relaxivity resulted from a **shortening of T₁**, which was detected as an increase in signal intensity in an MRI image,” (see column 36, lines 58 – 67 and Table V). Lauffer further describes the activation of complex 2 which is activated by collagenase (MMP-1). The MS is gly-ile. Release of the MM generates compound 9

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which is characterized by a higher binding affinity for HSA than prodrug 2. The altered signal in MRI permits the bioactivity to be imaged (see column 38, lines 1 – 50).

While it is noted that Lauffer does not specifically measure T_1 values for prodrug 2 and contrast agent 9, as they were done for prodrug 1 and contrast agent 8, it is the position of the examiner that prodrug 2 and contrast agent 9 effectively operate according to the same principle as that of prodrug 1 and contrast agent 8 (i.e. improved imaging upon cleavage of MS due to higher relaxivity), and thus would inherently function due to a reduction in T_1 times upon cleavage at the MS by MMP enzyme. For example, both contrast agents share the same qualities of greater HSA affinity and improved imaging upon MS cleavage, and thus absent evidence to the contrary, it is interpreted that the improved imaging of prodrug 2/contrast agent 9 upon cleavage by MMP is inherently a result of shortening of T_1 times, as is the case for prodrug 1/contrast agent 8.

Regarding the claimed functional property of T_1 time, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. The claims are descriptive and thus would be an inherent property of the claimed composition. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int.

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1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 19 – 22 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lauffer *et al.* (US 6,709,646) in view of Netzel-Arnett *et al.* (*Biochem.*, 1993, 32, p. 6427-6432), for reasons set forth in the Office Action mailed 7/12/2007.

Applicant argues on pages 10 – 11 of the Response that “Lauffer fails to teach cleavage of the MMP active peptide from the composition and subsequent change in T_1 in order to turn "on" the chelator. Netzel-Arnett has been cited for teaching specific MMP peptides. However, it fails to make up the deficiency of Lauffer because it also fails to teach activatable chelator that exhibits a change in T_1 in order to turn "on" the chelator.”

This is found non-persuasive. The inherent reduction in T_1 values in prodrugs/contrast agents disclosed by Lauffer is discussed above.

Conclusion

No claims are allowed at this time.

Although Applicant's arguments as set forth in the aforementioned Response have been fully considered, they are deemed unpersuasive. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS